REMARKS

This Reply is in response to the Office Action dated January 16, 2003. This Reply is filed along with a petition for a one-month extension of time and authorization to charge the required statutory fee to Deposit Account No. 50-0951.

Claims 42-69 were pending at the time of the Office Action. In the Office Action, claims 42-69 were rejected and claims 46 was objected to.

In this Reply, portions of the specification and claims 42-69 have been amended. No new matter has been added. The amended specification and claims are shown in a section entitled Marked-Up Version To Show Changes using standard underlining and bracketing format to highlight the changes made.

Applicant's counsel (the undersigned) wishes to thank the Examiner for a helpful teleconference which took place on April 10, 2003. During the teleconference issues relating to the Abstract, the issue regarding the Examiner's assertion of possible "new matter", and the cited art as compared to the claimed invention was discussed.

The Examiner raised "new matter" objections in paragraph 6 and the related 35 U.S.C. 112, first paragraph rejection based on the introduction of the term "diverse" in the specification and claims in the preliminary amendment filed on October 28, 2002. In response, Applicant has addressed these new matter objection and related claim rejections by removing all recitals of the term "diverse" in the specification and replacing "diverse" with "different types" as in "different types of molecules" in the claims. Explicit support for the phrase "different types of molecules" can be found on page 3, line 23 of Applicant's specification.

In paragraph 11 of the Office Action the Examiner raised several 35 U.S.C. 112, second paragraph claim rejections. The amendments made to the claims are believed to address and overcome all 35 U.S.C. 112, second paragraph rejections.

Turning to rejections based on art, claims 42-50 and 52-69 were rejected to under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,207,369 to Wohlstadter et al. Claim 51 was rejected under 35 U.S.C. 103(a) as being obvious over Wohlstadter et al. in view of Egholm et al. (Nature, 1993, 365: 566-567).

Claims 42-69 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 6,197,503 in view of Wohlstadter et al. Claims 42-69 were also rejected under the judicially created doctrine of

obviousness-type double patenting as being unpatentable over claims 1-45 of U.S. Patent No. 6,448,064 in view of Wohlstadter et al.

According to the Examiner:

Wohlstadter et al disclose an integrated biosensor system for the simultaneous detection of a plurality of diverse targets, the system comprising: at least one sampling platform including a plurality of receptors, said receptors including at least one protein receptor and at least one nucleic acid receptor (Column 24, lines 52-67) and an integrated circuit detector system having a plurality of detection channels (i.e. light detectors) for detecting electromagnetic signals related to binding events occurring at said plurality of receptors said detection channels each including at least one detector (Column 14, lines 10-24 and Column 14, line 45 – Column 15, line 63).

Before reviewing the cited art, Applicant will first review the claimed invention as now recited in amended claim 42. Amended claim 42 recites an photoluminescence-based integrated biosensor system for the simultaneous detection of a plurality of different types of targets. The system includes at least one sampling platform, the sampling platform including a plurality of receptors, the plurality of receptors including at least one protein receptor and at least one nucleic acid receptor. At least one excitation source of electromagnetic radiation at a first frequency is provided for irradiating the receptors. Electromagnetic radiation at a second frequency which is different from the first frequency is emitted by receptor/target combinations in response to irradiation when at least one of the targets are bound to one or more of the receptors. (see page 10, lines 19-28). An integrated circuit detector system having a plurality of detection channels is provided for detecting electromagnetic radiation at the second frequency, the detection channels each including at least one detector.

As noted in Applicant's background, while some disclosed photoluminescent-based biochip systems provide several detection channels, such as U.S. Patent No. 6,197,503, these systems are designed to use only <u>one</u> specific type of bioreceptor at a time, such as either nucleic acid or antibody probes. See also the following disclosed biochips which employ only one type of bioreceptor probe:

[1] S. P. A. Fodor, J. L. Read, M. C. Pirrung, L. T. Stryer, A. Lu, D. Solas, Science, 251, 767(1991).

[2] R.C. Anderson, G. McGall, and R.J. Lipshutz, in *Microsystem Technology in Chemistry and Life Science*, A. Manz and H. Becker, Eds, Springer Verlag, Berlin, pp. 117-129, (1998)

[3] M. Schena, D. Shalon, R. W. Davis, and P. O. Brown, Science, 270, 467 (1995)

[4] P. A. E. Piunno, U. J. Krull, R. H. E. Hudson, M. J. Damha, and H. Cohen, Anal. Chim. Acta, 228, 205 (1995).

[5] T. Vo-Dinh, B. J. Tromberg, G. D. Griffin, K. R. Ambrose, M. J. Sepaniak and E. M. Gardenhire, Appl. Spectrosc., 5, 735 (1987).

[6] T. Vo-Dinh, G.D. Griffin and M. J. Sepaniak, in O. S. Wolfbeis, Ed., *Fiber Optic Chemical Sensors and Biosensors*, CRC Press, Boca Raton, Florida (1991).

[7] P. Kumar, R. C. Wilson, J. J. Valdes and J. P. Chambers, Materials Science and Engineering, C1, 187 (1994).

[8] M. Eggers, M. Hogan, R. K. Reich, J. Lamture, D. Ehrlich, M. Hollis, B. Kosicki. T. Powdrill, K. Beattie, S. Smith, R. Varma, R. Gangadharam, A. Mallik, R. Burke and D. Wallace, 17, 516 (1994).

[9] O. S. Wolfbeis, Ed., *Fiber Optic Chemical Sensors and Biosensors*, CRC Press, Boca Raton, Florida (1991).

[10] T. Vo-Dinh, N. R. Isola, J.P. Alarie, D. Landis, G.D. Griffin, S Allison, Instrumentation Science & Technology, 26, 503 (1998).

While these earlier photoluminescent based biochip systems may be used for detecting either an individual or a plurality of a particular biochemical species on a single chip at the same time (e.g., in detecting one or more polynucleotides or in detecting one or more polypeptides), they were not devised to detect multiple biochemical species at the same time on the same chip, such as the simultaneous detection of polypeptides and polynucleotides on a single chip. Thus, these systems are unsuitable for simultaneous multidetection of a plurality of different types of targets.

Assay procedures using DNA probes is often referred to in the art as the "Southern Blot" and procedures using antibody probes is often called the "Western Blot". Due to protocol differences between "Southern Blot" and "Western Blot" assay, combined assays have been thought to not be possible by those having ordinary skill in the art primarily due to incompatibilities in assay protocol, such as pH, temperature and reagents.

Beginning on page 67 of Applicant's specification, EXAMPLE 3 entitled MULTIFUNCTIONAL BIOCHIPS describes the preparation and operation of a biochip having both DNA and antibody probes bound to a single sampling platform. Therein, a hybrid experimental protocol is described which permits these different probe types capable of detection of different types of targets to be bound to a common sampling platform and simultaneously assayed. Measurements described were performed using the biochip device demonstrating the simultaneous detection of the HIV1 gene and a gene from *Mycobacterium tuberculosis* (TB) using DNA probes, as well as the IgG protein and the cancer p53 antigen using antibody probes. Figure 4 shows the simultaneous detection of HIV, TB and Goat IgG protein using the HIV DNA probe (4 channels corresponding to the first row of the biochip), TB DNA probe (second row), and antibody probe for Goat IgG (fourth row).

Wohlstadter discloses electrochemiluminescence (ECL) materials and methods for producing patterned multi-array, multi-specific surfaces for use in diagnostics, such as for detecting or measuring an analyte of interest. Electrodes for ECL assays are also provided. Materials and methods are also disclosed for the chemical and/or physical control of electrically conducting domains and reagent deposition for multiply specific testing procedures.

Electrochemiluminescence (ECL) is the phenomena where an *electrically* excited species emits a photon. Species from which ECL can be induced are termed ECL labels and are also referred to herein as TAGs. ECL labels are generally organometallic compounds where the metal is from, for example, the noble metals of group VIII, including Ru-containing and Os-containing organometallic compounds. According to col. 47, lines 45-56:

ECL labels for use according to the present invention can be selected from among ECL labels known in the art (see Section 2.2, above, and U.S. Pat. No. 5,310,687). The ECL label may comprise, for example, a metal-containing organic compound wherein the metal is selected from the group consisting of ruthenium, osmium, rhenium, iridium, rhodium, platinum, palladium, molybdenum, technetium and tungsten. Suitable linking chemistry for preparing ECL TAG reagents is well known and disclosed, for example, by Bard et al. (U.S. Pat. Nos. 5,310,687 and 5,221,605). The means of attachment of the ECL label to a binding reagent may be covalent and/or noncovalent.

Fundamental to ECL-based detection systems is the need for an electrical potential to excite a suitable ECL label to emit a photon. An electrical potential waveform is generally applied across an electrode surface, typically a metal surface, and a counter electrode. The ECL label is promoted to an excited state as a result of a series of chemical reactions triggered by the

electrical energy received from the working electrode. The excited ECL label emits a photon as it relaxes to a lower energy state. Thus, the metal-containing organic ECL labels disclosed by Wohlstadter require *electrically energy* to be applied and absorbed to emit photons which can be detected and analyzed. The metal-containing organic compounds used as ECL labels are not adapted to photoluminesce.

Moreover, an environment conducive to ECL is taught by Wohlstadter for electochemoluminescence based detection. For example, col. 50, line 2-10 disclose the following:

> Suitable ECL assay medium are known in the art. Such an assay medium advantageously includes a molecule that promotes ECL of an ECL label, including but not limited to oxalate, NADH, and most preferably tripropylamine. Such a "promoter" molecule can be provided free in solution, or can be provided by prior linkage to or by production at (e.g., as a product of a chemical reaction) the PMAMS surface, a monolayer on the surface, the binding domain, the electrode surface, a binding reagent, and/or an ECL label, etc.

Photoluminescent based detection system, such as Applicant's claimed invention requires appropriate protocol as well as structures which absorb incident electromagnetic radiation (photons) and in response emanate electromagnetic radiation at a frequency different from the incident electromagnetic radiation. The frequency translation permits filtering of the incident radiation while allowing the emanated radiation to pass to the detector. Exemplary photoluminescent tags, such as some suitable for use with the claimed invention, are disclosed on page 25, line 31 to 33:

> Non-radioactive labels include, for example, ligands such as biotin or thyroxin, as well as enzymes such as hydrolases or peroxidases, or the various chemiluminescers such as luciferin, or fluorescent compounds like fluorescein and its derivatives.

Wohlstadter does not disclose or suggest Applicant's claimed photoluminescence based-system as recited in amended claim 42. First, Wohlstadter does not disclose or suggest Applicant's claimed excitation source of electromagnetic radiation as Wohlstadter's ECL based system requires *electrical* stimulation. Although regarding claim 52 the Examiner asserts that "Wohlstadter et al. disclose the biosensor comprising at least one excitation source selected from the group consisting of light emitting diode and diode array (column 29, lines 40-59)" Applicant respectfully notes that this portion does not mention light emitting diodes or a diode array as it relates only to light detectors, such as a photomultiplier tube, photodiode or CCD. The heading for column 29, lines 40-59 is appropriately titled "5.5. Light Detection".

Second, Wohlstadter does not disclose or suggest Applicant's claimed system which emits electromagnetic radiation at a second frequency different from the first (excitation) frequency in response to irradiating with excitation radiation when at least one of the plurality of different types of targets are bound to the plurality of receptors. Instead, *electrical* stimulation from a suitable electrode structure and waveform generator is used by Wohlstadter to trigger the emission of electromagnetic radiation.

In view of the many differences between the claimed invention and Wohlstadter, Applicant submits that amended claim 42 and its respective dependent claims are patentable over Wohlstadter. Method claims 68 and 69 which include limitations parallel to those recited in amended claim 42 are patentable for analogous reasons.

Claims 42-69 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 6,197,503 in view of Wohlstadter et al. Claims 42-69 were also rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-45 of U.S. Patent No. 6,448,064 in view of Wohlstadter et al.

According to the Examiner:

> Wohlstadter et al teach a motivation to utilize both protein and nucleic acid probes (receptors) i.e. facilitates the binding analysis of multiple and different analytes (Column 24, lines 52-59). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the patent probes by utilizing both protein and nucleic acid probes (receptors) as instantly claimed for the expected benefit of facilitating the binding analysis of multiple and different analytes as taught by Wohlstadter et al) (Column 24, lines 52-59).
>
> It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the patent sensing elements by utilizing both protein and nucleic acid sensing elements (receptors) as instantly claimed for the expected benefit of facilitating the binding analysis of multiple and different analytes as taught by Wohlstadter et al (Column 24, lines 52-59).

Applicant respectfully disagrees with both above double patenting rejections as explained below. U.S. Patent No. 6,197,503 and closely related U.S. Patent No. 6,448,064 disclose photoluminescent-based systems and methods for target identification. Wohlsadter discloses electrochemiluminescence based systems and methods for target identification. Thus, the respective references pertain to non-analogous art which notwithstanding their technical

incompatibility, would prevent one having ordinary skill in the art from coming to an inventor's attention in considering his problem.

Moreover, even if combined, Wohlstadter with either patent mentioned above would be inoperable. As noted above, Wohlstadter's receptors include a special protocol and electrochemiluminescent tags which are stimulated by *electrical* energy, not by photons. Thus, a hypothetical system formed by combining Wohlstadter's electrochemiluminescent receptors with either of the above patents which disclose photoluminescent-based systems, would not work at all as no photoluminescent output would be produced by illuminating Wohlstadter's electrochemiluminescent probes. Accordingly, the Examiner's double patenting rejections should be removed.

Applicant has made every effort to present claims which distinguish over the cited art, and it is believed that all pending claims are in condition for allowance.

However, Applicant requests the Examiner to call the undersigned after review of this Reply if the Examiner determines that any clarification is necessary to permit issuance of a Notice of Allowance.

Respectfully submitted,

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